Prof. Feldmann

Immunotherapy and other novel therapies

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Although no true breakthroughs occurred, publications during the 12-month period of this review added substantial definition to certain novel immunotherapies potentially applicable to the treatment of rheumatoid arthritis. Overall, this period witnessed maturation in the field of biologic interventions. Clinical trials provided further data needed to assess the efficacy of high-dose intravenous γ-globulin therapy in patients with systemic juvenile rheumatoid arthritis, and extended uncontrolled experience with interferon-γ in adult rheumatoid arthritis was obtained. An intriguing immunostimulant and antiviral drug, isoprinosine (inosine pranobex), failed in a scientifically rigorous trial in rheumatoid arthritis. Provocative insights into totally new approaches surfaced in additional reports from a variety of immunologic areas. Although seemingly distal to rheumatoid arthritis, these papers are cited because their further development or adaptations could reach a stage where clinical trials in rheumatoid arthritis are warranted.

Current Opinion in Rheumatology 1991, 3:369–372

Intravenous gammaglobulin therapy

Diseases for which high-dose intravenous γ-globulin therapy might be effective continue to proliferate. In a pilot study, seven of eight patients with treatment-resistant active juvenile rheumatoid arthritis, including systemic features, responded to a regimen similar to that in standard use for idiopathic thrombocytopenic purpura and other autoimmune disorders [1••]. Although open in design, most of the clinical outcome variables measured changed substantially, lending credibility to a conclusion that the intervention did indeed modify the disease. Improvement in fairly objective parameters, including the erythrocyte sedimentation rate and hemoglobin and albumin levels, were noted as well. The major problems with intravenous γ-globulin therapy seem to be monetary and logistic. Although the mechanism(s) responsible for the salutary effect remains elusive, additional evaluations of intravenous γ-globulin therapy in juvenile rheumatoid arthritis clearly appear to be indicated.

Pulse methylprednisolone or nitrogen mustard therapy

Although practiced not infrequently by certain experienced clinical rheumatologists, there is little literature on pulse treatment with methylprednisolone or nitrogen mustard. Thus, the review from the Cleveland Clinic Foundation is of importance [2•]. Both methodologic details and clinical and immunologic sequelae of high-dose intravenous pulse steroid and chemotherapy are detailed in a nonjudgmental fashion in this article. Based on their experience and the data displayed in the independent reports cited, the efficacy to toxicity ratio of nitrogen mustard appears to be acceptable for patients whose rheumatoid arthritis is refractory to more conventional approaches. The ready availability of mustard to rheumatologists would seem to justify further attention to this relatively neglected area of therapeutics, if a truly scientific format is followed.

Recombinant interferon-γ

Subcutaneous administration of recombinant interferon-γ as a potential treatment for rheumatoid arthritis has exhibited a discordant record in clinical studies to date. All uncontrolled trials have been short term, and although improvement has been described, benefit occurred in only two of the four placebo-controlled studies. Thus, the extended, open-label, 2-year follow-up of patients who participated in a prospective double-blind US multicenter trial is of interest [3•]. At 1- and 2-year follow-ups, 57% and 38% of the patients, respectively, remained on the agent. Improvement, compared to study entry, was evident in perhaps one third of the patients at 1 year and in 15% to 20% at 2 years. Systemic side effects (fever, chills, headache, nausea, diarrhea, and local reactions at the injection site), so troublesome in the short-term studies, seemed to abate, with only fever being a significant problem.

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Unfortunately, plaudits stop here. A number of major weaknesses make the study extremely difficult to interpret. Concurrent therapy with a gamut of drugs was permitted; the majority of patients were receiving nonsteroidal anti-inflammatory drugs, prednisone, and one of several so-called remittive regimens (gold, penicillamine, hydroxychloroquine, and even gold plus hydroxychloroquine). Even more confounding is the variable decrease in dose and frequency of interferon-γ that these patients received. It is likely that less exposure to the agent explains the better "tolerability" to the therapy. It is much more difficult to identify the drugs that were responsible for the improvement in this cohort.

Isoprinosine fails

The past decade has seen a series of putative immunoenhancer and antiviral agents surface as dualistic approaches for the curtailment of rheumatoid arthritis. Levamisole and amiprilose were two of the more widely touted drugs of this genre. During this period, another candidate known by a variety of names, including isoprinosine, inosine pranobex, inosiplex, and even methisoprinol slowly matured along this pathway. Lymphocyte stimulatory and antiviral properties were defined, but unfortunately most of the work was outside of the boundaries of peer-reviewed journals. Purportedly beneficial effects in rheumatoid arthritis appeared a number of years ago in an open study, prompting a careful, large-scale scrutiny within a double-blind, placebo-controlled format at the prestigious Center for Rheumatic Disease in Glasgow [4•]. Unfortunately, no significant improvement in any disease variable was noted in this 24-week trial. Equally intriguing was the fact that no evidence of spontaneous improvement in the disease occurred in the placebo limb, unlike the response to placebo in several recent trials in the United States. Are the Scots less suggestible, or has the so-called "placebo effect" been exaggerated recently?

Misoprostol: a gastroenterologic bequeathment to rheumatologists?

Pioneering, but often overlooked, work performed two decades ago elucidated striking anti-inflammatory properties for prostaglandins at pharmacologic doses in the adjuvant model of arthritis. In a variety of contexts, additional tantalizing properties for prostaglandin analogues have surfaced and engendered interest in their potential role in the treatment of immunologically mediated inflammatory arthritis [5•]. The most extensively studied candidate is misoprostol, the prostaglandin E_1 analogue now widely used to thwart nonsteroidal anti-inflammatory drug–induced gastropathic bleeding. An additional impetus to this theory has been several disclaimers of the "Vane hypothesis," *ie*, that prostaglandins are the major inciters of inflammation and their attenuation explains the efficacy of nonsteroidal anti-inflammatory drugs in inflammatory arthritis. Now that the precise mechanism of action of nonsteroidal anti-inflammatory drugs seems to have fallen into a "black hole," the once-antithetical possibility that prostaglandins might be clinically useful anti-inflammatory drugs is being considered. How this might be accomplished is a mystery. Could high ambient levels of prostaglandins inhibit macrophage or polymorphonuclear leukocyte functions, such as chemotaxis? Alternatively, could this feat be accomplished by immunoregulatory actions? *In vitro*, misoprostol has been reported to suppress lymphocyte proliferative responses. *In vivo*, misoprostol administration promoted the ability of humans to retain renal allografts. Further exploration into the possibility that prostaglandin E_1 analogues alter T-cell processes could bring about a new therapeutic dimension for patients with rheumatoid arthritis far beyond their action on the gastric mucosa.

Biologic inhibitors

The new frontier of intervention into autoimmune disease by specific, targeted biologic products (the plenitude, purity, and specificity of which are tightly insured by production via recombinant technology) continues to emerge. Potential applications, including osteoarthritis as well as rheumatoid arthritis, were recently reviewed by Hess [6•]. In terms of actual development, recent media attention has been devoted largely to a recombinant protein able to specifically inhibit the alleged central culprit in rheumatoid arthritis: interleukin-1. Paralleling this effort has been the purification of a natural inhibitor of another cytokine, tumor necrosis factor [7•]. Although the relevance of tumor necrosis factor and the biologic outcome of its banishment by a monospecific inhibitor remain in doubt, the isolation of interleukin inhibitors strengthens the probability that interleukin-mediated processes all involve precise cell surface receptors, and abrogation of the activity can be achieved by intervening with either the factor or its surface receptor.

The recent elucidation of a contra-interleukin-2 cytokine in the mouse [8•] further illustrates this theme. Based on the importance of T cells and probably interleukin-2 in the pathogenesis of the collagen model of rheumatoid arthritis, clones of T cells from collagen-immunized mice were probed and soon were found to secrete a factor that specifically antagonized interleukin-2-mediated pathways *in vitro*. Clinical assessment in the model revealed that inflammation could be reduced by injecting this protein. Although the exact biochemical nature of this adversarial product is uncertain, extrapolation of this approach to future treatment of rheumatoid arthritis can be envisioned.

Another report [9•] interjected caution into these approaches. While specific biologic antagonists for the immune system are being designed, often in "high-tech" fashion, naturally occurring counterparts are being elucidated as well. The existence of these naturally occurring contra molecules could argue that treatment with "designer molecules" would be superfluous and therefore ineffective. The recognition that autoantibodies of the IgG isotype capable of neutralizing the activity of interleukin-1 can be found in the sera of some patients with rheumatoid arthritis [9•] would argue that in certain stages of the disease, the body has already at least partially checkmated the process. Thus, additional therapeutic intervention would be biologically effete. Unidimensional attacks on aberrant immune pathways might have a limited effect on the underlying disease process.

Another example of a highly targeted approach is the use of a novel recombinant fusion protein with impressive specificity for the high-affinity interleukin-2 receptor. DAB_{486} interleukin-2 is a conjugate consisting of a portion of interleukin-2 joined to a diphtheria toxin fragment. This amalgam enables the hybrid species to interact as a ligand with the cell surface receptor for interleukin-2 and then deliver a lethal hit. Activated T cells express the interleukin-2 receptor, causing the molecule to be therapeutically appealing. Recent evaluation in adjuvant arthritis indicated that use of the protein was capable of suppressing both the induction and established stage of this model [10•]. By inference, these data strongly imply that interleukin-2-positive cells orchestrate a major portion of the pathogenesis of this disease. A theoretic concern with the use of this diphtheria conjugate to treat autoimmune disease in humans is their ubiquitous prior exposure to diphtheria vaccines, *ie*, that circulating antibodies to diphtheria might latch on and capture the immunologic missile before it could encounter the target cells. To address this potential liability, rats were preimmunized to diphtheria before the attempted induction of adjuvant arthritis. Even in these rats, where appreciable titers of diphtheria antibodies were found, the interleukin-2 receptor immunotoxin was effective. Inceptual feasibility work in rheumatoid arthritis was begun, and additional information regarding prospects for this approach should soon be available.

Hypothetical vaccination strategies also reside within the realm of targeted biologic therapies. Candidate autoantigens have been identified, including type II collagen and heat shock protein in rheumatoid arthritis. Schemes by which antigen-specific immunosuppression can be achieved have also been established, such as intravenous T-line cell inoculation. Earlier work showed that intravenous injection of antigen-coupled mononuclear cells or erythrocytes could abort an immune response to the antigen. Type II collagen coupled cells, injected intravenously, were used to attenuate the onset of adjuvant arthritis, demonstrating that intrinsically similar pathways operate in both the collagen and adjuvant models. Practicality, however, was lacking in this approach. More recently, investigators have unearthed another approach harkening back to older literature that cited peroral allergen administration as capable of expurgating atopic responses. For example, ingestion of poison ivy was claimed to be a way to alleviate contact sensitivity to this stimulus. The basic tenant is that gut lymphoid tissue is preferentially primed towards suppression of immune responses. Recent work has shown that experimental allergic encephalomyelitis and collagen arthritis can be prevented by peroral administration of myelin basic protein and type II collagen, respectively. Innovative experiments by Zhang *et al.* [11••] have shown that type II collagen ingestion can also downregulate adjuvant arthritis, duplicating the earlier results with collagen-coupled cells. Additional experiments revealed that immunosuppression was antigen specific and capable of being adoptively transferred with cells that were probably T suppressor in nature [11••]. The safety and simplicity of this vaccination protocol have been sufficiently compelling to warrant study in humans, seeking to ascertain whether curtailment of autoimmune disease in humans can be achieved by this approach. Major unanswered questions at present include 1) whether the human immune system recapitulates that of the mouse and therefore can be downregulated by oral antigen delivery, and 2) whether an established immune process, as is operative in autoimmune disease, can be quiesced by oral antigen intake.

Ideas for potential biologic approaches do not come solely from molecular biology laboratories. Harris and Sledge [12•] recently pinpointed in print the intriguing phenomenon that artificial hip replacement in patients with rheumatoid arthritis consistently results in sustained abatement of inflammation in the joint, whereas a similar outcome is not evident with knee replacement. In their opinion, the major differences in the two procedures relate to the complete absence of residual cartilage after a hip replacement, whereas patellar cartilage remains in a total knee joint replacement. Does the lack of cartilage explain the alleviation of synovitis after hip replacement? This experience seems sufficiently provocative to warrant further scrutiny into the precise nature of the provocative material in cartilage. Is it collagen? Is it proteoglycan? Is it possibly even a sequestered infective agent or by-product?

References and recommended reading

Papers of special interest, published within the annual period of review, have been highlighted as:

- • Of interest
- •• Of outstanding interest

1. •• SILVERMAN ED, LAXER RM, GREENWALD M, GELFAND E, SHORE A, STEIN LD, ROIFMAN CM: Intravenous gamma globulin therapy in systemic juvenile rheumatoid arthritis. *Arthritis Rheum* 1990, 33:1015–1022.

Dramatic results, albeit in an uncontrolled trial.

2. • DANAO T, SEGAL AM: Pulsed suppressive treatment in rheumatoid arthritis: intravenous methylprednisolone and nitrogen mustard. *J Rheumatol* 1990, 17:893–899.

Good overview of these alternative, unproven approaches.

3. • CANNON GW, EMKEY RD, DENES A, COHEN SA, SAWAY PA, WOLFE F, JAFFER AM, WEAVER AL, COGEN L, GULINELLO J, KENNEDY SM, SCHINDLER JD: Prospective two-year followup of recombinant interferon-γ in rheumatoid arthritis. *J Rheumatol* 1990, 17:304–310.

Methodologic flaws make it difficult to accept a conclusion of efficacy.

4. • BRZESKI M, MADHOK R, HUNTER JA, CAPELL HA: Randomized, double blind, placebo controlled trial of inosine pranobex in rheumatoid arthritis. *Ann Rheum Dis* 1990, 49:293–295.

Probably the last we will hear of this compound.

5. • NICHOLSON PA: Recent advances in defining the role of misoprostol in rheumatology. *J Rheumatol* 1990, 17(suppl 20):50–53.

Speculative but interesting.

6. • HESS EV: Cytokine inhibitors and osteoarthritis. *J Rheumatol* 1990, 17:1123–1124.

Concise and up-to-date coverage.

7. • SECKINGER P, VEY E, TURCATTI G, WINGFIELD P, DAYER J-M: Tumor necrosis factor inhibitor: purification, NH_2-terminal amino acid sequence and evidence for anti-inflammatory and immunomodulatory activities. *Eur J Immunol* 1990, 20:1167–1174.

Illustrative progress report.

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"Star Wars" attack on disease.

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Doomsday for biotechnology?

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Delineation of a dimension with widely ranging therapeutic potential.

11. •• ZHANG ZJ, LEE CSY, LIDES O, WEINER HL: Suppression of adjuvant arthritis in Lewis rats by oral administration of type II collagen. *J Immunol* 1990, 145:2489–2493.

Could treatment of autoimmune disease be this easy?

12. • HARRIS WH, SLEDGE CB: Total hip and knee joint replacement. *N Engl J Med* 1990, 323:801–807.

Possibly an important clue furnished by surgeons who keep their eyes open and minds engaged.

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